

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

BRAND NAME:	VELCADE
GENERIC NAME:	Bortezomib (PS-341)
DOSAGE FORM/STRENGTH:	3.5 mg Bortezomib and 35 mg Mannitol, USP, in Single-Dose Vials for Intravenous Injection
NDA:	21-602
INDICATION:	Relapsed and Refractory Multiple Myeloma
SUBMISSION TYPE:	NDA (New)
APPLICANT:	Millennium Pharmaceuticals, Inc.
SUBMISSION DATES:	January 21, April 8, April 10, April 16, 2003
OCPB DIVISION:	DPE-1 (HFD-860)
OND DIVISION:	DODP (HFD-150)
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I. Executive Summary

The Applicant seeks approval for VELCADE (bortezomib) Injection to be used in the treatment of patients with relapsed and refractory multiple myeloma. The proposed VELCADE dose is 1.3 mg/m² administered as a bolus intravenous injection twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (21-day treatment cycle).

A. Recommendations

The clinical pharmacology information provided by the Applicant for NDA 21-602 (VELCADE for Injection) is not acceptable from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) perspectives.

- The Applicant has not fully characterized the pharmacokinetics of bortezomib as a single agent at the proposed 1.3 mg/m² twice-weekly dose in patients with multiple myeloma.
- The Applicant has not evaluated the pharmacokinetics of bortezomib in hepatically impaired or renally impaired patients. Bortezomib is metabolized by liver enzymes and the Applicant should conduct a hepatic impairment study as a Phase 4 Commitment. Renal impairment is common among multiple myeloma patients. A renal impairment study is ongoing under the sponsorship of NCI/CTEP and the results of this study should be submitted as a Phase 4 Commitment.
- The Applicant has not conducted any formal pharmacokinetic study to evaluate the potential drug-drug interactions (DDI) between bortezomib and commonly co-administered medications in multiple myeloma patients. *In vitro* human microsomal studies indicate that bortezomib is primarily a substrate of CYP 3A4. The Applicant should conduct DDI studies as a Phase 4 Commitment.
- The Applicant has not justified the use of 1.3 mg/m². The increased toxicity in this dose group when compared to the 1 mg/m² and lack of additional benefit

calls for further investigations. Further, lack of correlation between proteasome inhibition and response rate (based any criteria) questions the target dose of 1.0 mg/m² or higher. It might be prudent for the applicant to explore lower than the dose of 1.0 mg/m², such as 0.7 mg/m².

The Applicant should address the Phase 4 Commitments (pp. 2), incorporate the OCPB labelling recommendations as outlined in section VI of this Review (pp. 36) in VELCADE package insert and address Comments 1-8 (pp. 3).

Please forward the Phase 4 Commitments (pp. 2), Comments 1-8 (pp. 3), and OCPB labeling recommendations (pp. 36) to the Applicant, and Comments 1-4 (pp. 4) to the Medical Reviewer.

B. Phase 4 Commitments

1. You should conduct a study to characterize the pharmacokinetics (PK) of bortezomib as a single agent at the 1.0 mg/m² and 1.3 mg/m² twice-weekly doses in at least 12 patients (per dose level) with multiple myeloma during Cycle 1 and subsequent Cycles. The patients should have normal to mild renal function (creatinine clearance values ≥ 50 ml/min). This study will also address the time-dependent changes in the PK of bortezomib as a single agent.
2. As bortezomib is metabolized by the liver, you should conduct a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study in patients with hepatic impairment to adequately provide dosing recommendations for this special patient population in the labeling for VELCADE. Please submit the study protocol for Agency review.
3. You should conduct a study to evaluate the PK and PK/safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction. Please submit the study protocol for Agency review.
4. You should conduct PK and PK/PD (pharmacokinetics/pharmacodynamics) studies to examine the potential for drug-drug interactions between bortezomib and drugs that are inhibitors (e.g., ketoconazole), or inducers (e.g., rifampicin) of cytochrome P450 3A4. You should also collect adverse reactions noted in this study and evaluate any relationship between plasma levels and adverse reactions.
5. You should evaluate the contribution of cytochrome P 450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using *in vitro* systems (microsomes, hepatocytes, liver tissue, etc.). Based on the results of this *in vitro* study, additional drug-drug interaction studies may be required.

Liver microsome study indicated that bortezomib did not inhibit midazolam and testosterone at a reasonable concentration. However, in this study midazolam concentration used was 10- fold higher than the optimal concentration for this type of study. Testosterone is not a sensitive probe for this type of study. On the other hand, the induction study with hepatocytes indicated that 2.5 μ M concentration (close to clinical concentration) of bortezomib inhibits CYP 3A4 activity to 35% of the control. Although it was an induction study, the side product was an inhibition profile. We like to request a phase 4 commitment to evaluate the inhibition potential

of bortezomib for CYP 3A4 using human liver microsomes with optimal midazolam concentration. If bortezomib significantly inhibits CYP 3A4 in *in vitro* study, the Applicant may need to conduct a clinical drug interaction study to evaluate the interaction between bortezomib and midazolam or other CYP 3A4 substrate.

6. Please provide your plan and projected completion time for the above recommended studies.

C. Comments [To the Applicant]

Clinical Pharmacology Comments:

1. As long as you are committed to conduct pharmacokinetic/pharmacodynamic (PK/PD) in renally and hepatically impaired patients, no mass balance study is required. However, to adequately label bortezomib, we recommend that you collect urine and feces samples from some patients receiving bortezomib as a monotherapy in any of your ongoing studies to determine how much drug-related species are excreted in these biological specimens. The results of this analysis will be incorporated under the CLINICAL PHARMACOLOGY/Pharmacokinetics-Excretion section of package insert for VELCADE.

2.

3. You have performed *in vitro* permeability studies using Caco2- monolayers with a high permeability positive control (propranolol) and low permeability negative control (Lucifer Yellow) and you concluded that bortezomib is not a substrate of P-gp. In the absence of a P-gp substrate as a positive control, it is not possible to confirm these results. Please, submit the *in vitro* permeability studies you performed with vinoplatin, a P-gp substrate, to the Agency for review.
4. You plan to perform population pharmacokinetic analyses on the data collected during your ongoing Phase 3 study (M34101-39) in multiple myeloma patients. Please submit these analyses to the Agency for review.
5. Bortezomib is likely to be prescribed in patients with end-stage renal disease undergoing hemodialysis. We recommend that you perform *in vitro* studies to determine the dialyzability of bortezomib through standard dialysis membranes.

Pharmacometrics Comments:

6. You have not adequately justified the selection of the 1.3 mg/m² dose. The lack of convincing dose-effectiveness relationship limits the ability to suggest rational dosing for VELCADE. Very clearly, the 1.3 mg/m² group had higher toxicity, but no advantage for the response rate (effectiveness) was evident. In the study 025, in a considerable fraction of patients the dose was reduced to 1 mg/m² from 1.3 mg/m². One could speculate that in clinical practice this fraction could be even more. It is only prudent for

the sponsor to find the rational dose towards more meaningful labeling of VELCADE. Approach to finding a 'rational' dose for VELCADE needs some discussion. The analysis presented by this reviewer did not establish that proteasome inhibition is a good predictor of the response rate. In fact some patients with negligible inhibition (assuming the inhibitory effect is appropriately measured) responded, based on the SWOG criteria. Hence targeting a dose of 1.0 mg/m² itself is questionable. It is possible that lower doses could have produced similar response rates as for the 1.3 mg/m² dose, but with lower toxicity. Closer look at the SWOG responses showed that the majority of patients achieved this response by the second cycle, and few more by the fourth cycle. The applicant should conduct a randomized dose ranging study including 0.7 mg/m², 1.0 mg/m² and 1.3 mg/m². If the patients who receive the lower doses do not respond (according to the SWOG criteria) by the fourth cycle, they might be transferred to the next higher dose group. Also, the applicant should collect pharmacokinetic data in future studies to enable rational dosing strategies. Such a study should provide valuable data to select an optimal dosing scheme for labeling. The application should consider such a study.

7. Interestingly, given a high enough doses (with respect to proteasome inhibition) there seems to be wide range of effects ranging from below zero to about 100% inhibition, in studies M34100-024 and -025. One practical reason could have been that although the protocol specified a 1-hour sample, it is possible that the actual time could be off. Given the rapid disposition phase of VELCADE, such large variability is possible should the sampling time be mislabeled. The Applicant should explain this result.
8. Two points need to be noted regarding body size based dosing: a) between patient variability and b) mechanistic reasoning. a) Even given the little PK information, the variability seems to be as high as 80% for the important PK parameters like initial concentration and clearance (Study DM98-194, dose=1.6 mg/m², n=13). If this estimate of between subject variance is accurate, it is not clear why VELCADE needs to be dosed based on body surface area. It is unlikely that body size explains significant portion of the unexplained variability. b) The toxicity seems to be dose dependent and no explanation is given by the sponsor whether the dose needs to be given on a per m² basis. If the drug is not well distributed into poorly perfused tissues (e.g., adipose), then indeed the dose should not be based on total body size. The Applicant should substantiate the need for body size based dosing. Future studies should use the appropriate dosing scheme.

Comments [To the Medical Reviewer]

1. The pharmacokinetic (PK) information provided in this NDA submission at the proposed 1.3 mg/m² twice-weekly bortezomib dose in multiple myeloma (MM) patients is limited to one patient in Study M34100-024 and eight patients ranging in creatinine clearance values from 31 to 169 ml/min in Study M34100-025. In both studies, plasma levels were available only up to 2 hours after dosing; the complete PK bortezomib profile has not been adequately characterized. The PK data obtained in Study DM98-194 are irrelevant to this NDA submission. The PK data for this study were generated at higher doses (1.45-2.0 mg/m²) in 24 patients with advanced malignancies; the assay method was not adequately validated (no quality control data available). The PK data submitted at 1.0 mg/m² (n=17) and 1.3 mg/m² (n=5) dose in Study M34100-027 are interim data, generated in 21 patients with solid tumors and confounded by the presence of gemcitabine. No assay validation was submitted for these interim PK data. At the

present time, the package insert for VELCADE will include the limited PK information [estimated median (range) maximum plasma concentration] obtained in eight patients with MM at the proposed 1.3 mg/m² twice-weekly bortezomib dose in the pivotal Phase 2 Study M34100-025.

2. As bortezomib is primarily metabolized by the liver. The package insert for VELCADE will include precaution statement for use of VELCADE in hepatically impaired patients until a study in this special population is conducted and results are submitted to Agency for review.
 3. The results of the NCI/CTAP renal impairment study will be incorporated in the VELCADE package insert after completion and submission of the study. At the present time, since the efficacy and safety of bortezomib were evaluated during the pivotal Phase 2 Study M34100-025 in patients having creatinine clearance values ranging from 13.8 to 220 ml/min, a precaution statement will be included in the package insert for the use of VELCADE in patients with creatinine values less than 13 ml/min and patients on hemodialysis.
 4. Bortezomib is primary a substrate of CYP 3A4. The package insert will also include a precaution statement for the use of VELCADE in combination with other drugs that are substrates, inhibitors, or inducers of 3A4 until drug-drug interaction studies are conducted and results are submitted to the Agency for review.
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III. List of Abbreviations

AUC	Area under the plasma concentration-time curve from zero to infinity
C ₀	Estimated plasma concentration from the extrapolation of the initial distribution phase of the log-linear plasma concentration versus time plot to time = 0.
ChT:T	Chymotrypsin-like to trypsin-like activity
CL	Total body clearance
CV	Coefficient of variation (%CV=100*SD/mean)
CYP	Cytochrome P450 enzymes
DLT	Dose limited toxicity
DPE	Division of Pharmaceutical Evaluation
DODP	Division of Oncology Drug Products
GLP	Good laboratory practices
hr	Hours
IV	Intravenous
LC/MS/MS	Liquid chromatography/tandem mass spectroscopy
MM	Multiple myeloma
MTD	Maximum tolerated dose
min	Minutes
n	Number of patients
NC	Not calculated
ng	Nanogram
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
OND	Office of New Drugs
26S	26S Proteasome sub-unit
%	Percent
PD	Pharmacodynamics
PK	Pharmacokinetics
SD	Standard deviation
t _{1/2}	Terminal half-life
vs	Versus
V _{ss}	Steady state volume of distribution
V _z	Volume of distribution based on the terminal phase

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IV. Summary of Clinical Pharmacology and Biopharmaceutics Findings

PS-341 is a modified dipeptidyl boronic acid derived from leucine and phenylalanine specially designed to reversibly inhibit the chymotrypsin site of the 26S proteasome enzymatic activity. The 26S proteasome is a large protein complex (comprised of the 20S core and 19S activator) whose purpose is to degrade proteins targeted by ubiquitination for destruction. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signaling cascades within the cell, ultimately resulting in cell death.

The Applicant proposes to use VELCADE (bortezomib, PS-341) in the treatment of patients with relapsed and refractory multiple myeloma (MM) at a proposed dose of 1.3 mg/m² to be administered as a bolus intravenous (IV) injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (21-day treatment cycle) for a maximum of eight treatment cycles.

The efficacy and safety information submitted in this NDA is derived from two open-label, prospectively-designed, multi-center, non-comparative, Phase 2 studies, Studies M34100-025 (pivotal, n=202) and M34100-024 (supportive, n=54), conducted in relapsed and refractory MM patients. The primary efficacy variable was the overall response rate, where a responder was defined as a complete remission (CR), partial response (PR), or minor response (MR). Overall, the most commonly reported adverse events were nausea, diarrhea, fatigue, thrombocytopenia, constipation, vomiting, anorexia, pyrexia, peripheral neuropathy (including sensory and peripheral neuropathy aggravated), and anemia.

The biomarker or surrogate endpoint measured during clinical pharmacology and clinical studies (DM98-194, 98-104A, LCCC9834/00-31, M34100-025, and M34100-024) is the inhibition of the 26S proteasome enzyme activity. The results of these studies demonstrate that mean percent proteasome inhibition activity is consistently higher at 1 hr than at 6 hr or 24 hr after dosing on any day of dosing and higher on last day of dosing than the first day at 1, 6, or 24 hr after dosing. The relationship between percent proteasome inhibition activity and dose indicate that the optimum PS-341 dose may be between 1.0 mg/m² and 1.3 mg/m². At the 1.3 mg/m² dose, the 1-hour mean percent inhibition on Day 1 Cycle 1 is higher than the corresponding value of Cycle 7 (70.5% vs 55%). The results also demonstrate that there is no difference in the mean percent proteasome inhibition whether PS-341 is administered once weekly, twice weekly for two weeks, or twice weekly for four weeks. At doses of 1.45-2.0 mg/m², a poor correlation is noted between the percent proteasome inhibition activity at 1, 6, and 24 hr after dosing on Day 1 and estimated maximum plasma concentration (C₀) (r=0.07), suggesting that at these doses, the percent proteasome inhibition may have reached a plateau. C₀ was estimated as the zero-time intercept of log concentration/time plot. The Co-administration of dexamethasone may slightly increase the inhibition of 26S proteasome activity by PS-341. Mean percent inhibition of 26S proteasome activity at 1 hr after dosing on Day 1 of Cycle 1 is 73% after the 1.3 mg/m² dose (n=4) alone therapy compared to 70.5% (n=11) for the combination of 1.3 mg/m² dose and dexamethasone.

In vitro studies with human liver microsomes and human cDNA-expressed CYP isozymes indicate that PS-341 undergoes oxidative metabolism by 1A2, 2C9, 2C19, 2D6 and 3A4 enzymes. The major metabolic pathway is deboronation of PS-341 to form two metabolites which are subsequently hydroxylated to several metabolites. Deboronated PS-341 metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low

compared to the parent drug. Unchanged PS-341 is the only drug-related entity measured in clinical pharmacology studies and used to assess the pharmacokinetic parameters and exposure/ response relationships.

The Applicant has not characterized the disposition of PS-341 in humans. Animal data indicate that PS-341 is eliminated via both renal and hepatic routes (Nonclinical Summary). In intact rats, 38.6% of the administered radioactivity is excreted in the feces, 21% in the urine, and 6.1% in expired air.

The Applicant analyzed PS-341 concentrations in plasma using a _____ method with protein precipitation as an extraction procedure and ^{14}C -PS-341 as an internal standard. The method was adequately validated according to the Good Laboratory practices (GLP) for Studies M34100-024 and -025; however, for Study DM98-194, the method was not adequately validated (no quality control data available). The lower limit of quantitation (LOQ) was _____ with a linear standard curve over _____ ng/ml for Studies M34100-024 and -025 and _____ ng/ml for Study DM98-194.

The pharmacokinetic (PK) information provided in this NDA submission at the proposed 1.3 mg/m^2 twice-weekly PS-341 dose in multiple myeloma (MM) patients is limited to one patient in the Phase 2 Study M34100-024 and eight in the Phase 2 Study M34100-025. In both studies, plasma levels are available only up to 2 hours after dosing. Plasma samples collected at 24 hr after dosing were below LOQ (_____ g/ml). Although the assay method was adequately validated in these studies, a complete PK PS-341 profile was not possible to determine. In Study M34100-025, the estimated maximum plasma concentration (C_0) averages 625 ± 446 (CV=71%) in seven patients with MM patients ranging in creatinine clearance (CLcr) values from 31 to 79 ml/min; one patient with CLcr value of 169 ml/min has no estimated C_0 value. The percent proteasome inhibition activity determined at 1 hr in the eight patients after dosing ranges from _____. The one patient in Study M34100-024 has an estimated C_0 value of 232 ng/ml at the 1.3 mg/m^2 dose.

The pharmacokinetics (PK) information obtained in Phase 1 Study DM98-194 was generated in 24 patients with advanced malignancies at higher doses than the proposed dose, 1.45 mg/m^2 (n=4), 1.6 mg/m^2 (n=13), 1.8 mg/m^2 (n=2), and 2.0 mg/m^2 (n=5)), but the assay was not adequately validated (no quality controls data).

The PK data submitted at 1.0 mg/m^2 (n=17) and 1.3 mg/m^2 (n=5) doses in the ongoing Phase 2 Study M34100-027 are interim data generated in patients with solid tumors and confounded by the presence of gemcitabine. As this is an interim report, an assay validation report was not submitted.

PS-341 exhibits linear PK over the weekly IV bolus doses of 1.45 mg/m^2 (n=4), 1.6 mg/m^2 (n=13), 1.8 mg/m^2 (n=2), and 2.0 mg/m^2 (n=5) in patients with advanced malignancies (Study DM98-194). The binding of PS-341 to human plasma proteins is linear over the concentration range of 10-1000 ng/ml and averaged $83 \pm 3.0\%$.

PS-341 may accumulate upon twice weekly administration. Interim PK data from the ongoing Phase 2 Study M34100-027 reveal that exposure to PS-341 when given in combination with gemcitabine is higher on Day 8 than on Day 1 of Cycle 1. PS-341 AUC increased 2.1-fold and its CL decreased by 40% on Day 8 compared to Day 1 at the

1.3 mg/m² PS-341 dose. This accumulation may be due to time-dependent kinetics or due to the effect of gemcitabine on PS-341 exposure. Accumulation of PS-341 as a monotherapy during a specific cycle and from cycle to cycle is not known.

The Applicant has not evaluated the effects of age, gender, and race on the PK of PS-341. A population PK analysis of the data from the ongoing phase 3 Study M34101-039 in multiple myeloma patients may assess these effects.

The Applicant has not conducted any clinical pharmacology study to examine the pharmacokinetics of PS-341 in special populations such as pediatric, geriatric or renal- or hepatic-compromised populations. The package insert will include a precaution statement for the use of VELCADE in renally and hepatically impaired patient until studies in these special populations are conducted and results are submitted to Agency for review (see Phase 4 Commitments).

The Applicant has not conducted any clinical pharmacology studies to evaluate the potential for drug-drug interactions between PS-341 and potential concomitant medications. The package insert for VELCADE reflects this fact.

PS-341 is primary a substrate of CYP 3A4. Approximately, 60% of PS-341 was metabolized by 3A4 isoenzyme in 60 minutes. In isolated isoenzyme microsomes, 2D6, 2C19, 1A2, and 2C9 metabolized 50%, 33%, 23%, and 21% of PS-341 in 60 minutes, respectively. There may be a potential for PS-341 clearance to increase or decrease when it is coadministered with drugs that are potent inhibitors or inducers of 3A4 (e.g., ketoconazole, rifampicin). The package insert will include a precaution statement for the use of VELCADE in combination with drugs that are substrates, inhibitors or inducers of 3A4 until drug-drug interaction studies are conducted and results are submitted to the Agency for review (see Phase 4 Commitments).

In vitro enzymatic human microsomal studies indicate that PS-341 is a weak inhibitor of CYP activity with IC₅₀ values of >30 µM for 1A2, 2C9, 2D6, and 3A4 enzymes. PS-341 is unlikely to affect the metabolic clearance of concomitantly administered drugs that are substrates of these enzymes. However, PS-341 may have a potential to inhibit 2C19 activity. An IC₅₀ value of 18 µM was obtained at *in vitro* substrate concentrations (S-mephenytoin) two-fold higher than optimum concentrations (400 µM vs < 200 µM, respectively). PS-341 may have a potential to decrease the metabolic clearance of drugs that are substrate of 2C19 activity. The Applicant should repeat the *in vitro* microsomal studies at appropriate S-mephenytoin concentrations (< 200 µM) to properly assess the inhibitory potential of PS-341 on 2C19 activity (see Comments to the Applicant). It is also noted that the *in vitro* midazolam concentrations was 10-fold higher than the optimum recommended substrate concentrations (100 µM vs < 10 µM, respectively) for *in vitro* inhibition studies. As midazolam is a more sensitive substrate than testosterone, the Applicant should also repeat the *in vitro* studies at appropriate midazolam concentrations (<10 µM) to properly assess the inhibitory potential of bortezomib on 3A4 activity (see Phase 4 Commitments).

Although PS-341 does not induce the activities of 3A4 and 1A2 in primary cultured human hepatocytes. In this system (viz., cultured human hepatocytes), PS-341 inhibited the 3A4 activity by 35% of the control at PS-341 concentration of 2.5 µM (see Phase 4 Commitments).

PS-341 may nor be a substrate for p-glycoprotein (see Comments to the Applicant).

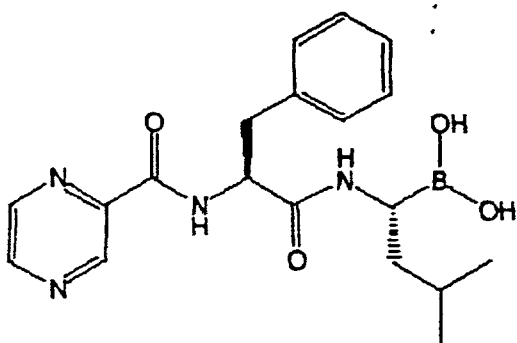
V. Question-Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

PS-341 (Bortezomib) is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. The chemical name for PS-341 is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid. PS-341 has the following structural formula (Fig.1):

Figure 1: Chemical Structure of PS-341



Molecular Weight: 384 g/mole

Molecular Formula: $C_{19}H_{25}BN_4O_4$

PS-341 molecule has two pK_a values determined at 25°C and zero ionic strength: $pK_{a1} = 0.7 \pm 0.2$, and $pK_{a2} = 8.6 \pm 0.1$. In the pH range ~1.0 to 8.0, the molecule is neutral, and at pH values above ~8.5, the molecule is negatively charged. The intrinsic *n*-octanol/water partition coefficients for PS-341 are 100.8 for the neutral species and < 0.1 for the negatively charged species. The solubility of PS-341, as the monomeric boronic acid, in water is 3.3-3.8 mg/ml in a pH range of 2.0-6.5. PS341 contains two chiral centers per monomeric unit. The drug product is a single stereoisomer.

Formulation

VELCADE (bortezomib, PS-341) for Injection will be supplied as single-dose vials for intravenous (IV) administration. Each vial contains a sterile lyophilized powder of 3.5 mg bortezomib with 35 mg mannitol, USP. The drug product is the cyclic mannitol boronic ester form of the drug, derived from lyophilization in the presence of the excipient mannitol (see Fig. 2). The drug product is to be reconstituted in 0.9 % sodium chloride for injection. The reconstituted drug product is an equilibrium mixture of the PS-341 boronic acid and the PS-341 mannitol boronic ester (see Fig. 3).

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Figure 2: Structure of PS-341 Drug Product (Applicant's)

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Figure 3: Structure of Saline-Reconstituted PS-341 Drug Product (Applicant's)

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What is the proposed mechanism of drug action and therapeutic indication?

PS-341 is a novel antineoplastic agent specifically designed to inhibit 26S proteasome activity by binding reversibly to the chymotryptic site of the 20S core of the enzyme ($K_i = 0.62$ nM) (Nonclinical Summary). The 26S proteasome is a large protein complex (comprised of the 20S core and 19S activator) whose purpose is to degrade proteins targeted by ubiquitination for destruction. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signaling cascades within the cell, ultimately resulting in cell death. The Applicant proposes the following mechanisms of action for PS-341 in multiple myeloma:

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The Applicant proposes the use of VELCADE (bortezomib, PS-341) in the treatment of patients with relapsed and refractory multiple myeloma (MM). Multiple myeloma is a B-cell malignancy of plasma cells and represents the second most common hematological malignancy after non-Hodgkin's lymphoma. Drugs approved for the treatment of MM include melphalan (1992), carmustine (BCNU, 1977) and cyclophosphamide (1959) in the United States, and epirubicin in Europe.

What is the proposed dosage and route of administration?

What efficacy and safety information contributes to the assessment of clinical pharmacology data?

Efficacy and safety information is derived from two open-label, prospectively-designed, multi-center, non-comparative, Phase 2 studies conducted in relapsed and refractory MM patients, M34100-025 (pivotal) and M34100-024 (supportive). All patients enrolled in both studies received PS-341 as an IV bolus twice weekly for two weeks followed by a 10-day rest (21-day cycle) period for up to eight treatment cycles.

- ***Pivotal Study M34100-025:*** This was conducted at 14 centers in the United States in 202 patients with relapsed and refractory multiple myeloma (MM). Patients ranged in age from 34 to 84 years, 121 males and 81 females (81% Whites). The primary objective of the study was to evaluate the efficacy and safety of PS-341 (1.3 mg/m²) alone, or given in combination with dexamethasone (40 mg) subsequent to inadequate response to PS-341 monotherapy. During the first two treatment cycles, all patients received PS-341 alone at a dose of 1.3 mg/m². Thereafter, dexamethasone was added to the patient's treatment regimen, for patients with a suboptimal response to PS-341 alone. Patients received 20 mg dexamethasone orally four times per week on each day of and day after PS-341 administration for two consecutive weeks (i.e., for every dose of 1.3 mg/m² PS-341 patients received a total of 40 mg of dexamethasone).
- ***Supportive Study M34100-024:*** This was conducted at 10 centers in the United States in 54 patients with relapsed and refractory multiple myeloma (MM) to evaluate the response rate following treatment with PS-341 1.0 or 1.3 mg/m² alone. Patients ranged in age from 30 to 84 years. During the first two treatment cycles, all patients were randomly assigned to receive PS-341 alone at doses of 1.0 mg/m² (n=28, 14 males and 14 females) or 1.3 mg/m² (n=26, 9 males and 17 females). Thereafter, dexamethasone was added to the patient's treatment regimen, for patients with a suboptimal response to PS-341 alone. Patients received 20 mg dexamethasone orally four times per week on each day of and day after PS-341 administration for two consecutive weeks (i.e., for every dose of 1.3 mg/m² PS-341 patients received a total of 40 mg of dexamethasone).

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**Table 1. Demographic Characteristics (All Patients; Studies M34100-025 and M34100-024)
(Applicant's)**

	Study M34100-025 (1.3 mg/m ²)			Study M34100-024		
	by Cohort and Overall			by Dose Group and Overall		
Characteristic / Statistic	Cohort 1 (n=78)	Cohort 2 (n=124)	Total (n=202)	1.0 mg/m ² (n = 28)	1.3 mg/m ² (n = 26)	Total (n = 54)
Sex [N, (%)]						
N	78	124	202	28	26	54
Male	46 (59)	75 (60)	121 (60)	14 (50)	9 (35)	23 (43)
Female	32 (41)	49 (40)	81 (40)	14 (50)	17 (65)	31 (57)
Race [N (%)]						
N	78	124	202	28	26	54
White	62 (79)	102 (82)	164 (81)	25 (89)	20 (77)	45 (83)
Black	8 (10)	13 (10)	21 (10)	3 (11)	3 (12)	6 (11)
Asian	5 (6)	0 (0)	5 (2)	0	2 (8)	2 (4)
Other	3 (4)	9 (7)	12 (6)	0	1 (4)	1 (2)
Age (years)						
N	78	124	202	28	26	54
Mean (± SD)	60 (9.5)	60 (9.2)	60 (9.3)	64 (11.7)	60 (12.2)	62 (12.0)
Median	59	59	59	65	61	63
Minimum, Maximum	39, 84	34, 83	34, 84	39, 82	30, 84	30, 84
KPS [N (%)]						
N	76	120	196	28	26	54
60	9 (12)	10 (8)	19 (10)	2 (7)	2 (8)	4 (7)
70	10 (13)	11 (9)	21 (11)	1 (4)	2 (8)	3 (6)
80	34 (45)	40 (33)	74 (38)	8 (29)	8 (31)	16 (30)
90 or 100	23 (30)	59 (49)	82 (42)	17 (61)	14 (54)	31 (57)
Creatinine clearance (mL/min)						
N	78	123	201	28	26	54
Mean	83.8	77.7	80.0	72.3	88.8	80.2
SD	34.43	35.31	35.01	31.10	40.12	36.35
Median	79.6	70.4	73.9	71.2	81.8	74.5
Minimum, maximum	28.6, 220.9	13.8, 180.5	13.8, 220.9	22.9, 130.8	37.4, 183.4	22.9, 183.4

KPS (Karnofsky performance score)

The primary efficacy variable was the overall response rate, where a responder was defined as a complete remission (CR), partial response (PR), or minor response (MR). Overall, the most commonly reported adverse events were nausea, diarrhea, fatigue, thrombocytopenia, constipation, vomiting, anorexia, pyrexia, peripheral neuropathy (including sensory and peripheral neuropathy aggravated), and anemia.

B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The biomarker or the surrogate endpoint measured during clinical pharmacology and clinical studies (*DM98-194, 98-104A, LCCC9834/00-31, M34100-024, and M34100-025*) is the inhibition of the 26S proteasome enzyme activity. The 26S proteasome is a large protein complex (comprised of the 20S core and 19S activator) whose purpose is to degrade

proteins targeted by ubiquitination for destruction. Within the 20S core are three proteolytic activities: 1) trypsin-like, 2) post-glutamyl, and 3) chymotrypsin-like. PS-341 specifically inhibits the chymotrypsin-like activity of 20S proteasome.

In these studies, blood samples were collected to measure the 26S proteasome inhibition activity after PS-341 administration.

The chymotrypsin-like activity of the 26S proteasome was measured using an *ex-vivo* spectrofluorometric assay method as described by Lightcap et al (Lightcap et al, Proteasome inhibition measurements: clinical application, Clinical Chemistry 2000; 46 (5):673-83]. The assay measures cleavage of a synthetic fluorogenic substrate, Suc-Leu-Leu-Val-Tyr-7-amino-4-methyl-coumarinamide (AMC). By binding to the enzyme's active site, PS-341 inhibits binding and proteolysis of the substrate, producing a diminished signal. The ratio of 26S proteasome chymotrypsin-like to trypsin-like activity (ChT:T) on the proteasome enzyme was determined in the whole blood. The percent (%) proteasome inhibition activity was calculated relative to baseline (Day 1, Cycle 1) as: $100 * [(baseline\ ChT:T\ ratio - current\ ChT:T\ ratio) / (baseline\ ChT:T\ ratio + (0.35 * current\ ChT:T\ ratio))]$.

Study DM98-194 was a phase 1, single-center, dose-escalation, PK, and PD study designed to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of PS-341 in 53 patients with advanced malignancies. PS-341 was administered as an IV bolus **once weekly for four consecutive weeks** (on Days 1, 8, 15, and 22), followed by a 2-week rest period. Doses administered were 0.13 (n=4), 0.25 (n=2), 0.4 (n=2), 0.6 (n=2), 0.75 (n=2), 0.8 (n=3), 0.85 (n=2), 0.9 (n=2), 1.0 (n=2), 1.1 (n=2), 1.2 (n=2), 1.3 (n=2), 1.45 (n=6), 1.6 (n=13), 1.8 (n=2), and 2.0 (n=5) mg/m². Blood samples for determination of 26S proteasome inhibition activity in whole blood were collected from 45 patients immediately before and at 1, 6, and 24 hours after dosing on Days 1, 8, 15, and 22 of Cycle 1. Blood samples were also collected for determination of plasma profiles in 24 patients who enrolled at the highest dose levels pre-dose and at 0.16, 0.5, 1, 2, 4, 6, and 24 hours after PS-341 IV bolus administration. The PK of PS-341 were evaluated at the 1.45 mg/m² (n=4), 1.6 mg/m² (n=13), 1.8 mg/m² (n=2), and 2.0 mg/m² (n=5) doses.

Study 98-104A was a phase 1, dose-escalation, PD study designed to determine DLT and MTD of PS-341 in 43 patients with advanced solid tumors. PS-341 was administered as an IV bolus **twice weekly for two consecutive weeks** (on Days 1, 4, 8, and 11) followed by a 10-day rest period. Doses administered were 0.13 (n=3), 0.25 (n=4), 0.4 (n=5), 0.6 (n=4), 0.75 (n=3), 0.9 (n=6), 1.08 (n=3), 1.3 (n=3), and 1.56 (n=12) mg/m². Blood samples for determination of 26S proteasome activity in whole blood were collected from 31 patients immediately before and 1 and 24 hours after dosing on Days 1 and 8 and immediately before and 1 hour after dosing on Days 4 and 11, Cycle 1. The Applicant did not plan to evaluate the PK of PS-341 in this study.

Study LCCC9834/00-31 was a phase 1, dose-escalation, PK, and PD study designed to determine the MTD of PS-341 in 27 patients with hematologic malignancies. PS-341 was administered as an IV bolus **twice weekly for four consecutive weeks** (on Days 1, 4, 8, 11, 15, 18, 22, and 25) followed by a 14- to 17-day rest period. Doses administered were 0.40 (n=3), 1.04 (n=12), 1.2 (n=7), and 1.38 (n=5) mg/m². Blood samples for determination of 26S proteasome activity in whole blood were collected from 26 patients immediately before and 1 and 24 hours after dosing on Days 1, 4, 8, 11, 15, 18, 22, and 25 of Cycle 1. Although pharmacokinetic analyses were planned in the original protocol, the Applicant

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Table 2 Response rates in relapsed and resistant myeloma by regimen and population

Reference	Treatment	Population	N	CR (%) ^a	PR (%) ^c
6	VAD	Relapsed/ Resistant	67	2 (3%) ^b	39 (58%)
7	Gemcitabine	relapsed- refractory	16	6% (1/16)	18% (3/16)
8	Thalidomide	Relapse/ Resistant	60	0	17 (28%)
9	Thal + Dex	Relapse/ Resistant	44	0	24 (55%)
10	Thal + Dex	relapsed- refractory	77	0	18 (23%)
11	CC5013	Relapsed	24	0	7 (30%)
12	PSCT	Resistant <1y	27	2 (8%)	17 (62%)
13	PSCT	Relapse/ Resistant	120	(26%)	(55%)
14	Double PSCT	Relapse/ Resistant	135	(8-29%)	(50-70%)

^a CR per Blade definition except as noted ^b CR = complete disappearance of protein by electrophoresis ^c PR = 50% decrease in M protein

Response criteria in multiple myeloma The development of newer dose-intensive therapeutic options has led to new methods for the definition of response. Existing criteria for the assessment of disease response, based on some percentage of decrease in the myeloma protein, did not appear to predict outcome after high-dose therapy. In 1998, Blade, *et al* proposed more strict criteria for the assessment of complete response following high dose therapy.¹⁵ These criteria require the complete absence of myeloma protein by immunofixation techniques as well as by protein electrophoresis. Lahuerta JJ, *et al* subsequently published a retrospective study suggesting that the immunofixation status of the patients, but not the amount of M protein secreted, was correlated with survival and TTP.¹⁶ The responses to therapy of three hundred forty-four myeloma patients were retrospectively analyzed after myeloablative therapy followed by stem cell transplant. Response was simultaneously measured by both electrophoresis (EP) and immunofixation (IF). Patients who were IF negative showed a significantly better event-free survival (EFS) [35% at 5 years] and overall survival (OS) (72% at 5 years, median not reached) compared with any other response group (univariate comparison $P = 0.004$). In contrast, patients who remained IF positive, regardless of the quantity of the M protein, did not define a different prognostic subgroup, and therefore, the CR^(IF) response category was not shown to correlate with improved survival in this study in a post transplant population.

Relationship between response and survival: In an early study dealing with response to treatment in MM, Alexanian, *et al* reported that the median survival of patients who responded to melphalan was 41 months compared with 9 months in patients who did not respond.¹⁷ This study reported that the survival of patients treated with combination chemotherapy was directly correlated with the extent of reduction of paraprotein synthesis. However, a similar survival

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analysis carried out by Palmer et al (1989) failed to show such a correlation.¹⁸ Several other studies have also reported a lack of correlation between response and survival. Even with regimens such as high-dose melphalan-140 mg/m² and VAD, which produced CR in up to 25% of newly diagnosed patients, duration and survival were not prolonged in patients reaching CR as compared with those achieving PR.¹⁹

Regulatory implications: Durable complete responses may be considered to be evidence of clinical benefit in hematologic malignancies, however the Blade complete response criteria have not been validated as clinical benefit by the FDA. Under the subpart H "Accelerated Approval" regulations (CFR §314.510 Subpart H), marketing approval may be granted by the FDA "based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity." This surrogate endpoint must be "reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." Based on a literature review, additional clinical benefit analysis of the patients exhibiting a partial response including improved survival in these patients, and the advice of SGE practitioner consultants, the partial response rate was also considered to be a surrogate for clinical benefit.

3 Important Milestones in Product Development

Initial screening of the National Cancer Institute's (NCI) tumor cell lines revealed that PS-341 is active against a broad range of tumor types, prompting further exploration of the activity of PS-341 in cell culture and in murine and human xenograft models.^{20,21}

Regulatory History

August 25, 1998: IND ————allowed to proceed.

October, 1998: A phase 1 study in advanced cancer was initiated at ————

March 19, 2001: End of phase 1 meeting discussion points included design of the phase 2 studies, fast-track designation and designation of orphan drug status.

PS-341 was granted fast track designation based on the premise that the treatment of patients with relapsed and refractory MM represents an unmet medical need.

Phase 2 studies were initiated in February 2001 and completed in June 2002.

December 7, 2001: An end of phase 2 meeting was held to discuss the preliminary data obtained, the design of a randomized trial (M34101-039), and the potential for approvability of PS-341 under subpart H of the regulations.

September 4, 2002: An additional end of phase 2 meeting was held after completion of patient enrollment to study 025. Preliminary data analysis of the first cohort of 78 patients from study M34100-025 was presented in order to discuss accelerated approval of PS-341 to treat relapsed and refractory MM.

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December 2 2002: Pre NDA meeting to

- Provide evidence that phase 2 study results are reasonably likely to predict clinical benefit;
- Provide an update on status of the phase 3 trial and provide evidence that completion of this trial will not be affected by accelerated approval;
- Provide more complete characterization of phase 2 patient population to support unmet need;

January 21, 2003: NDA 21-602 filed with FDA

Significant Agreements between FDA and the Sponsor

May, 2002: The sponsor and FDA entered into an agreement under a Special Protocol Assessment regarding the design and analysis of an international, multi-center, randomized, open-label phase 3 study of PS-341 versus high dose dexamethasone. For approval under 21CFR 314.500 Subpart H, the sponsor would have to demonstrate superiority in time to progression. For full approval, the sponsor would also have to demonstrate superiority in a clinical benefit endpoint including infections and skeletal events.

4 Other Relevant Information

This drug is not approved in other countries.

5 Important Issues with Pharmacologically Related Agents

This drug is the first in its class of proteasome inhibitors to be granted marketing approval. Dr. Susan Lindquist, a Howard Hughes investigator formerly at the University of Chicago, and now the Director of the Whitehead Institute at MIT, has published a paper which raised the concern that proteasome inhibitors might potentially be implicated in the development of prion diseases.²² Dr. Lindquist's research has focused primarily on yeast prions, and the concerns raised were purely theoretical, and thus far there has been no clinical evidence to suggest that this is a significant safety concern.

III Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

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1 CMC

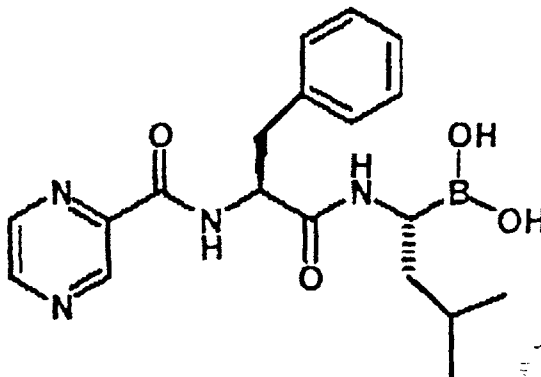
Bortezomib is a modified dipeptidyl boronic acid. VELCADE™ (bortezomib) for Injection is available for intravenous injection only, as a sterile lyophilized powder in single-dose vials containing 3.5 mg bortezomib and 35 mg mannitol, USP. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid. The molecular weight is 384.24. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8mg/mL in a pH range of 2-6.5.

The chemical structure is shown in Figure 1:

Figure 1: Structure of PS-341

Chemical Structure of PS-341

(Molecular formula: $C_{19}H_{25}BN_4O_4$; Molecular weight: 384.25 Daltons)



2 Non-Clinical Pharmacology

The following are excerpted from the pharmacology reviews and from the label.

2.1. Mechanism of Action

PS-341 (VELCADE) reversibly inhibits the chymotryptic proteolytic activity of the 20S-proteasome of mammalian cells. The 20S-proteasome binds with several regulatory proteins to create the 26S-proteasome complexes that hydrolyze proteins that have been marked for destruction by the ubiquitin enzyme cascade. This ubiquitin-proteasome system is responsible for essential elements of homeostatic control within the cell in G_0 and numerous processes

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through the course of the cell cycle. In replicating cells, when PS-341 inhibits this system, the cell cycle arrests at the transition of G₂-M. Inhibited cells then initiate apoptosis.

2.2. Non clinical pharmacokinetics

Single and multiple dose pharmacokinetics (PK) studies of PS-341 in rats and cynomolgus monkeys were conducted. After single dose IV administration to rats and cynomolgus monkeys, plasma concentrations of PS-341 declined in a biphasic manner with a rapid distribution phase followed by a longer terminal elimination phase. The terminal plasma elimination half-life in cynomolgus monkeys averaged 8 to 10 hours following a single dose. The area under the plasma concentration-time curve (AUC) increased in a dose-dependent manner over the tested dosage range of up to 1.2 mg/m² in both species. After multiple doses of PS-341 (twice weekly for 2 weeks followed by 1 week rest), there is a decrease in clearance that results in an increase in the terminal elimination half-life (t_{1/2}) and AUC (3-4 fold) in rats and cynomolgus monkeys suggesting drug accumulation.

2.3. Non clinical toxicology

2.3.1 Animal Studies:

In preclinical studies in the rat and primate species (Cynomolgus monkey, the most sensitive species on a weight-based dosage), the major target organs of toxicity of VELCADE included the gastrointestinal (dose-limiting emesis and diarrhea) and hematological/lymphoid (anemia, thrombocytopenia) systems, and peripheral nerves.

2.3.1.1 Single Dose Studies

Single-dose studies to evaluate cardiovascular safety in the Cynomolgus monkey suggest that cardiovascular collapse is the cause of death in these animals. All monkeys exhibited lethal effects from the 3.0 mg/m² single dose; in this species, the MTD is 1.2 mg/m². (In the mouse, the MTD dose is 3.0 mg/m².) In the primate, there is only a small margin between the MTD and the potentially lethal dose and this characteristic warrants caution. Hypotension was the most prominent toxicity, but associated with the hypotension were alterations in heart rate (tachycardia followed by bradycardia) and hypothermia. For single dose studies, reversal of toxicity in most target organs was observed following recovery with the exception of axonal degeneration of the sciatic nerve.

2.3.1.2 Repeat Dose Studies

In a 2-week twice-weekly repeated-dose IV toxicity study in rats with a 2-week recovery period, the MTD was 1.5 mg/m². A 4-week twice-weekly repeated dose IV toxicity study in monkeys with a 2-week recovery period was used in determining the safe starting dose and the target organs of toxicity for Phase 1 clinical trials. The MTD in the monkey was 0.8 mg/m² (0.067 mg/kg).

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Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, were conducted to characterize the chronic toxicity of PS-341 when administered by the chosen clinical route and regimen. The MTD in the 6-month rat study was 0.6 mg/m^2 (0.10 mg/kg) and, although not fully completed at this time, in the monkey the MTD appears to be 0.6 mg/m^2 (0.05 mg/kg).

In the rat toxicity studies, the principal target organs affected are dose-related hyperplastic mucosal changes throughout the gastrointestinal tract, decreased platelet counts sometimes associated with bone marrow hypocellularity, lymphoid tissue atrophy due to apoptosis of lymphocytes, and increased liver weight with hepatocellular hypertrophy and/or vacuolization. All these findings were partly or completely reversible within 8 weeks. The most important target organ was the GI tract where proliferative mucosal changes were the likely cause of death or moribund sacrifice (for unscheduled death animals) in repeated-dose toxicity studies in the rat. The pathogenesis of dosage-related decreased platelet counts is not known, but it is sometimes associated with visible bone marrow hypocellularity and may be myelosuppressive in origin. Hematopoietic effects were not severe and reversible at and below the MTD.

In the Cynomolgus monkey repeated-dose toxicity studies, the principal target organ effects were: sporadic but sometimes severe anemia and thrombocytopenia; GI intolerance characterized by emesis and diarrhea; decreased circulating lymphocyte counts; lymphoid tissue atrophy; renal tubular degeneration; myocardial necrosis; and neuropathy characterized by spinal cord degeneration and peripheral nerve axonal degeneration. Reversal of toxicity was observed following recovery with the exception of the axonal degeneration of the sciatic nerve and spinal cord. Peripheral (sciatic) nerve degeneration was observed in 2 of 10 animals at the high-dosage (1.2 mg/m^2) in the 4-week toxicity study. The mechanism of PS-341 induced neuropathy is not known.

Anemia and thrombocytopenia were seen at all dosages and caused premature sacrifice for 3 of 4 animals in the 9-month study. The pathogenesis of this change is not certain, but bone marrow hypocellularity was observed. Gastrointestinal intolerance was the most consistent dose limiting toxicity and the likely cause of moribund sacrifice for one early death animal without severe anemia and/or thrombocytopenia from the 9 month study. A histologic correlate for GI intolerance has not yet been described in the monkey.

In summary, the chronic dose MTD following 9 cycles (6-months) of administration of PS-341 in the rat was 0.6 mg/m^2 (0.10 mg/kg). In the monkey, following 14-cycles (9-months), the provisional MTD (pending full completion of the study) is 0.6 mg/m^2 (0.05 mg/kg). The proposed clinical dose and the dose for labeling is 1.3 mg/m^2 . The acute toxicity of VELCADE in animals is characterized by a steep dose-response with mortality seen at dosages modestly above the MTD. The cause of death at acutely lethal dosages is considered to be related to cardiovascular effects of hypotension and vascular changes. The safety margin expressed on the basis of dosage is less than one when comparing MTDs from comparable nonclinical studies to the human exposure. This margin is in the lower range for cytotoxic anticancer agents.

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Table 3: Relation of MTD to exposure for representative species

SPECIES	MTD (mg/m ²)	
	SINGLE DOSE	MULTI-DOSE
MOUSE	3.0	0.9 (IP DAILY)
RAT (S-D)	0.6	1.8 (TWICE WEEKLY X 2 WEEKS)
MONKEY	1.2	0.8 (TWICE-WEEKLY X 4 WEEKS)

Reviewer's Table

Distribution and Elimination

VELCADE is initially rapidly cleared following IV bolus administration with a distribution phase of less than 10 minutes. Mean terminal half-life (elimination phase) increased with increasing dose from 5.5 hours at 1.0 mg/m² to 15 hours at 2.0 mg/m² (in the -027 protocol when combined with gemcitabine).

Pharmacodynamic Assessment: Proteasome Activity

Proteasome inhibition was measured by percent inhibition of chymotrypsin protease activity on whole blood or leukocyte samples from patients receiving treatment with VELCADE. Proteasome inhibition averaged 50% (over 24 hours following a dose) over a wide range of C_{max} values from 10-100 ng/ml. At plus one hour, the mean percent inhibition was 56% with 1.0 mg/m² and 62% with 1.3 mg/m² IV bolus doses. The plasma level declined by approximately 50% over the 24 hour interval. VELCADE is a potent (0.6 nM K_i) and reversible inhibitor of the proteasome and showed no significant activity against the other enzymes or receptors tested at that concentration.

Reviewer's comment: Pharmacodynamic studies to date have not shown a correlation between proteasome inhibition by this assay and response or toxicity events. The relation of proteasome inhibition to clinical events has not been established. Studies evaluating the role of VELCADE as a "spindle poison" or tubulin inhibitor analogous to the actions of the vinca alkaloids or taxanes have not been reported (given VELCADE's neurotoxicity). Treatment-emergent tumor resistance has not yet been described in preclinical models. Multi-drug resistance (MDR) expressing tumor cells or tumors that express a number of tumor virulence-conferring mutations were not resistant to cell killing with PS-341 in a test system. VELCADE-induced proteasome inhibition has been measured in whole blood and peripheral blood mononuclear cells as a correlate for intracellular drug activity within tumor xenografts and other tissues. The sponsor has chosen a twice -weekly regimen of administration considering: the duration of pharmacodynamic (PD) effect (approximately 72 hours), the expectation that maximum tolerated dosage may produce maximal anti-tumor activity, and tolerability studies suggesting that dose intensity over time may be able to be maximized when proteasome activity is allowed to return toward baseline between doses.

Animal PK-PD Summary:

In the non-clinical toxicity studies, both PK and PD assessments were done. In the 14 week IV toxicity study in rats the mean AUC (0-24) and C_{max} at the MTD of 0.10 mg/kg(0.6 mg/m²) was

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145 hr*ng/mL and 10.7 ng/mL at week 14 with a mean inhibition of 26S proteasome (ChT:T) activity of 91%. The week 26 AUC(0-24) and Cmax values were 134 hr*ng/mL and 10.9 ng/mL, respectively, with a mean 26S inhibition of 83%. In the 9 month monkey toxicity study the MTD was the lowest dosage studied, 0.050 mg/kg (0.6 mg/m²), and resulted in mean AUC(0-24) and Cmax values of 83.1 hr*ng/mL and 48.2 ng/mL at week 38. The mean peak inhibition of 26S (ChT:T) activity was 75% at week 38 (9 months) for this dosage. These compare with the available PK data from cancer patients administered 1.0 mg/m² where the AUC(0-24) and Cmax were 53.7 hr*ng/mL and 139 ng/mL, respectively, and mean proteasome inhibition of 60-70% was achieved. Therefore, the safety margins on the basis of AUC are less than one, similar to the safety margin of less than one when compared on the basis of dosage (see below also).

Rodents: Sprague Dawley rats were administered PS-341 as a single dose, weekly x 8 and twice weekly for 2 weeks, and 26 weeks. The 9-cycle 26-week study is discussed in detail below. PS-341 was administered IV at 0.3, 0.6, and 1.2 mg/m² over 5 or 9 three-week cycles (i.e., twice-weekly administrations for 2-weeks followed by a 1-week rest period) to rodents. On Day 28/29, the high dosage was decreased from 1.2 to 0.9 mg/m² due to toxicity. Traditional toxicologic parameters, as well as neuropathological evaluations, toxicokinetic, and proteasome activity were assessed. PS-341-related mortality was observed at ≥ 0.9 mg/m² (day 50-day 197) and was due primarily to hematopoietic (bone marrow hypocellularity), gastrointestinal (hyperplasia and necrosis), and lymphoid system debilitation (lymphocytic depletion, atrophy, and necrosis of lymph nodes, spleen and thymus). Histopathological changes were observed in the heart (inflammation, hemorrhage, and necrosis), liver (hypertrophy and necrosis), lung (necrosis and inflammation), kidney (necrosis and degeneration), sciatic nerve (necrosis), and spinal cord (inflammation); similar findings were observed in scheduled deaths. Animals dosed ≥ 0.9 mg/m² surviving to week 26 (end of treatment), exhibited multifocal neurotoxicity including brain dilatation, and degeneration of dorsal and ventral root ganglia, peripheral nerves, and spinal cord. Chronic progressive nephropathy was generally observed at 26 weeks at all doses; males appeared to be more susceptible to kidney changes. Histopathological changes in cardiac tissue included increased incidence of perivascular necrosis (at ≥ 0.6 mg/m²), myocardial degeneration, hemorrhage, and inflammation. Thrombocytopenia was observed at all PS-341 dose levels. Following the 8-week recovery period, myocardial and vascular inflammation, cardiac necrosis and chronic progressive nephropathy were still observed at all doses; the incidence of findings was not dose-dependent. There appeared to be some indication of reversibility of other findings at this time. Monkeys were administered PS-341 as a single dose, for 24 hours, daily X 13 days, twice weekly for 2 weeks, twice weekly for 4 weeks and for 13-three week cycles. The 13-cycle study is discussed in detail below.

Monkeys: PS-341 was administered IV at 0.6, 0.9, and 1.2 mg/m² over 13 three-week cycles (i.e., twice-weekly administrations for 2-weeks followed by a 1-week rest period) to cynomolgus monkeys. PS-341-related mortality was observed at dosages ≥ 0.9 mg/m². The predominant findings in these animals were multifocal neurotoxicity (including brain necrosis and swelling, and degeneration of axons and myelin of dorsal root ganglia, peripheral nerves and spinal cord), severe anemia (bone marrow hypocellularity), thrombocytopenia, cardiotoxicity (necrosis, inflammation, and hemorrhage), and gastrointestinal intolerance (diffuse mucosal hyperplasia) and dehydration; similar findings were observed in scheduled deaths. Evidence of lack of neurological reflex was observed at multiple sites at all dose levels in animals which

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survived to 38 weeks (end of dosing period). The incidence of neurotoxicity was reduced following 8 weeks of recovery. The incidence of histopathological changes in cardiac tissue, including necrosis and inflammation was minimal and not dose dependent; the severity of cardiac findings was not reported. Kidney findings (hypertrophy/degeneration, glomerulonephropathy, inflammation and the presence of hyaline casts) were observed at ≥ 0.9 mg/m² PS-341; males appeared to be more susceptible to kidney changes. Lymphoid atrophy and/or necrosis was exhibited in thymus, spleen, lymph nodes and gut-associated lymphoid tissue. In addition, necrosis and atrophy of the gastrointestinal tract was observed in monkeys surviving to 38 weeks.

Conclusions: The primary toxicities of PS-341 appeared to be hematopoietic, gastrointestinal, cardiac, and neurological. Myocardial and vascular inflammation, cardiac necrosis and chronic progressive nephropathy were observed at all doses; the incidence of findings was not dose-dependent. There appeared to be some indication of reversibility of other findings.

Cardiotoxicity:

Cardiovascular safety pharmacology studies conducted in cynomolgus monkeys showed that administration of dosages ≥ 3.0 mg/m² PS-341 (twice the recommended clinical dose) resulted in initial physiologically significant heart rate elevations, which preceded a profound progressive hypotension, bradycardia, and moribundity 12-14 hours postdose. Increased heart rate and decreased mean arterial pressure were also observed at lower doses of PS-341 (≥ 1.2 mg/m² and ≥ 2.4 mg/m², respectively).

Neuropathy

Monkeys and rats were dosed for 13-three week cycles with a similar schedule as recommended for patients (twice weekly dosing for 2 weeks followed by 1-week rest). Neurotoxicity was multifocal and included brain necrosis and swelling and degeneration of axons and myelin of dorsal root ganglia, peripheral nerves, and spinal cord. Multifocal nerve degeneration of dorsal root ganglia, peripheral nerves and spinal cord was observed at ≥ 0.6 mg/m².

2.4. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. VELCADE could have a potential effect on either male or female fertility.

2.5. Pregnancy

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No clinical information exists about the safe use of VELCADE during pregnancy. No cancer patients were found to have become pregnant during the trials and no pregnant patients received VELCADE. Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest maternally tolerated dosages when administered during organogenesis. The highest maternally tolerated dosages were 0.05mg/kg (0.3mg/m²) in the rat and 0.025 mg/kg (0.3 mg/m²) in the rabbit. These dosages are approximately 0.2 times the clinical dose of 1.3mg/m², based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m²) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m², based on body surface area.

The pregnancy labeling category is D.

No placental transfer studies have been conducted with bortezomib. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

2.6. Nursing Mothers

It is not known whether bortezomib is excreted in human milk.

3 Drug Interactions

VELCADE is a substrate for both CYP3A4 and 2D6 enzymes. No formal study of drug-drug interactions has been conducted. VELCADE also may be a substrate for CYP 2C9, which might affect warfarin dosing. Please see the Clinical Pharmacology and Biopharmaceutics review of this NDA for further information.

4 Statistical Evaluation of Collective Evidence

The statistical portion of this NDA is part of the efficacy section (see section VI).

5 Human Pharmacokinetics and Pharmacodynamics

5.1. Pharmacokinetics

Pharmacokinetic (PK) data is not available at the proposed label dose of 1.3 mg/m² twice weekly as monotherapy or in combination with dexamethasone. Plasma levels for up to two hours post-exposure were available for exposure at other dose levels from 1.0 to 1.3 mg/m² and 1.45 to 2.0 mg/m². Drug clearance appears to be dose dependent but non-linear. Please see the Clinical Pharmacology and Biopharmaceutics review of this NDA for further information.

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5.2. Pharmacodynamics

Proteasome inhibition in tumor cells is the putative target of VELCADE. This inhibition is then expected to inhibit protein degradation resulting in altered intracellular levels of various proteins including regulatory and growth-promoting cytokines. This imbalance may be cytotoxic directly or through apoptotic responses. Inhibition is assayed by measuring the reduction of proteasome chymotrypsin (ChT) activity compared to trypsin (T) activity (ChT:T ratio) in circulating mononuclear white blood cells or red blood cells of patients. Over the entire range of C_{max} obtained, proteasome inhibition was approximately 60% of maximum over 24 hours on day 1 of the 1.3 mg/m² dose. At the 1.0 mg/m² dose, 56% inhibition was achieved. Proteasome inhibition data is very limited but did not correlate with any measures of toxicity. However, increasing the dose from 1.0 to 1.3 mg/m² twice weekly correlated strongly with increased diarrhea and nausea (see pharmacometrics review).

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IV Description of Clinical Data and Sources

1 Overall Data

The primary source for this sNDA review consisted of data and study reports submitted to the sNDA on study 025. Additional information was gained from the data submitted on study 024 and the phase 1 studies DM98-194 and 9834/00-31, literature sources cited in the footnotes, and bone marrow biopsy and aspirate samples provided by the sponsor at the request of the FDA.

2 Tables Listing the Clinical Trials

Table 4: Phase 1 Studies

Dates, Status	Design	Primary Objectives	Dose and Regimen	Patient Population	N
Study DM98-194 Phase 1 Study of PS-341 in Advanced Cancers					
Completed 10/07/98 – 12/20/01	Open-label, dose- escalation	Determine DLT, MTD, PK and PD of PS-341; evaluate relationship between toxicity and 20S proteasome inhibition peripheral blood lymphocytes; evaluate response to treatment	Dose escalation range: 0.13 – 2.0 mg/m ² IV bolus 1x per week for 4 weeks, 14-day rest period Each cycle is 35 days	Histologically confirmed malignancy for which there is no standard therapy	53
Study 98-104A Phase 1 Study of PS-341 in Advanced Malignancy					
Completed 2/8/99 – 10/02/00 1	Open-label, dose- escalation	Determine DLT, MTD, and PD of PS-341; evaluate relationship between toxicity and 20S proteasome inhibition in peripheral blood lymphocytes; determine inducibility of IκB degradation in lymphocytes; evaluate response to treatment	Dose escalation range: 0.13 – 1.56 mg/m ² IV bolus 2x per week for 2 weeks, 10-day rest period Each cycle is 21 days	Histologically confirmed malignancy for which there is no proven effective therapy	43
Study 98-104A: Phase 1 Study of PS-341 in Advanced Malignancy					
Completed 11/8/99 – 7/26/01 2 centers	Open-label, dose- escalation	Determine DLT, MTD, and PD of PS-341	Dose escalation range: 0.4 – 1.38 mg/m ² IV bolus 2x per week for 4 weeks, 17-day rest period Each cycle is 42 days	Histologically confirmed hematologic malignancy who are not candidates for conventional therapy	27

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Table 5: Phase 2 studies

Status, Study	Dates,	Study Design	Primary Objectives	Dose and Regimen	Patient Population	N
Study M34100-024, A Randomized, Open-Label, Phase II Study of Two Doses of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Failed to Respond to or Relapsed Following Front-line Therapy						
Completed	5/14/01 – 7/12/02	Randomized, Open-label, Multi-center	To determine the response rate (the combined CR + PR + MR) following treatment with PS-341 1.0 or 1.3 mg/m ² /dose monotherapy	1.0 or 1.3mg/m ² IV push 2x per week for 2 weeks, 10-day rest period Each cycle is 21 days Maximum of 8 treatment cycles	Multiple myeloma who failed to respond to or relapsed following front-line therapy	54
Study M34100-025, An Open-Label Phase II Study of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Relapsed Following Front-Line Therapy and Are Refractory to Their Most Recent Therapy						
Completed	2/26/01 – 6/12/02	Open-Label, Multi-center	To determine the response rate (the combined CR + PR + MR) following treatment with monotherapy PS-341	1.3 mg/m ² IV push 2x per week for 2 weeks, 10-day rest period Each cycle is 21 days Maximum of 8 treatment cycles	Multiple myeloma who relapsed following initial front-line therapy and refractory to most recent therapy	202

3 Postmarketing Experience

None – this product has not been previously marketed.

4 Literature Review

The sponsor conducted an extensive review of the literature. The FDA conducted an independent literature review, the FDA citations used in this review are found in the Reference section.

V Clinical Review Methods

1 How the Review was Conducted

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This review focused on the data submitted for study 025 in a refractory MM population. Data was analyzed in order to confirm the primary endpoint of complete response rates. Additional safety and efficacy information was obtained from study 024. Peter Bross, MD performed the efficacy review, Robert Kane, MD performed the safety review, Yong-Cheng Wang, Ph.D. performed the statistical review, and these reviews were combined. Ann Farrell, MD was the clinical team leader. Gang Chen Ph.D. was the statistical team leader. A consultation was obtained from the Division of Scientific investigation and the 2 sites that contributed the most patients to the study in the US were inspected. A separate statistical review was not performed. Two representatives from the Oncology Drug Advisory Committee (ODAC) and 2 additional oncologist consultants provided advice, after being cleared of conflict of interest. Bone marrow slides were obtained when available on the patients in complete remission and these slides were examined by the review team.

2 Overview of Materials Consulted in Review

The primary data was analyzed for consistency with the study reports and with selected case report forms (CRF's). Response rates were analyzed with respect to clinical study center for inconsistencies, and the Division of Scientific Investigation (DSI) was consulted to inspect study sites. The FDA DSI investigator examined the case report forms and compared them with source documents such as patients' charts to verify disease states, and with the sponsor's data printouts. The FDA obtained bone marrow aspirate and biopsy slides on most of the complete responders for microscopic analysis and review.

3 Overview of Methods Used to Evaluate Data Quality and Integrity

The primary data was analyzed for consistency with the study reports and with selected case report forms (CRF's). Response rates were analyzed with respect to clinical study center for inconsistencies, and the Division of Scientific Investigation (DSI) was consulted to inspect two study sites. The FDA DSI investigator examined the case report forms and compared them with source documents such as patients' charts to verify disease states, and with the sponsor's data printouts. The FDA obtained pathology slides of patients in complete remission to verify these results.

4 Were Trials Conducted in Accordance with Accepted Ethical Standards

This sponsor has asserted that the study was performed in accordance with standard operating procedures designed to ensure adherence to good clinical practice guidelines and ensure the ethical protection of the patients, as required by the following directives in operation at the time:

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1. Declaration of Helsinki, concerning medical research in humans ('Recommendations Guiding Physicians in Biomedical Research Involving Human Patients', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, 1996).
2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and Institutional Review Board (IRB) approval.

The investigator was to be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents were to be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files were to be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

5 Evaluation of Financial Disclosure

The sponsor certified that 128 investigators provided information that they had no significant proprietary interest in Millennium pharmaceuticals. Financial disclosure information for 13 investigators had not been received despite additional requests (including forms) which the sponsor states were issued to the investigators and follow-up telephone calls which were made to each study center in an effort to retrieve this information. However, the sponsor certifies that none of these 143 investigators had any financial arrangement with the sponsor whereby the value of the compensation could be affected by the outcome of the study.

The sponsor provided the following information regarding 3 investigators with a financial arrangement with or proprietary interest in Millennium pharmaceuticals:

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The research contracted to _____ was to perform a retrospective analysis of the _____ patient database in order to better understand the natural history of patients with multiple myeloma.

VI Integrated Review of Efficacy

1 Brief Statement of Conclusions

The sponsor submitted efficacy data on 256 patients treated in the phase 2 studies 024 and 025. Study 024 was a dose finding study with relapsed myeloma patients; and study 025 was designed to determine the response rates in relapsed and refractory myeloma patients. The patient population was heterogeneous and some patients were relatively lightly pretreated. When these lightly pretreated patients were excluded, the FDA concluded that the population could support the demonstration of efficacy in patients with relapsed and refractory myeloma. The primary efficacy endpoint was response rate, according to a variety of response criteria (see protocol review and introduction for a discussion of response criteria). The CR^{Blade} criteria was considered to be the currently accepted definition of complete remission in MM however have not yet been validated as *de facto* evidence of clinical benefit. The FDA was able to confirm a CR^{Blade} responses rate of 2.7% (95% CI 1%, 6%) in the relapsed and refractory population. These responses were accompanied by evidence of clinical benefit including increased hemoglobin and platelet counts, decreased transfusion requirements, and increasing physiologic immunoglobulins. CR^{Blade} The FDA confirmed that the median time of response duration was

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142 days for the CR+PR group, and the Kaplan-Meier estimate of the median duration of CR+PR was 365 days. Additional response analyses were performed to confirm a clinical benefit of treatment with PS-341. Twelve patients achieved a 100% reduction of the serum or urine M-protein for a median of 96 days. Five (41%) of these patients relapsed. A total of 30% of all patients achieved a CR or PR (50% improvement in M-protein). Partial responses were seen across a variety of subgroups including patients who had undergone transplant and high dose therapy, patients with elevated B-2 microglobulin, chromosome 13 deletions, and elderly patients. An exploratory analysis of survival by response category was performed, although this type analysis is methodologically flawed, which confirmed that the patients in the better response categories tended to live longer.

2 General Approach to Review of the Efficacy of the Drug

This review focused on the NDA data submitted for Millennium Pharmaceuticals study 024 and 025 including datasets, CRF's and study reports and other information on 256 patients with MM treated with PS-341. In addition, the FDA obtained bone marrow aspirate and biopsy specimens on patients in complete response.

3 Detailed Review of Trials by Indication

3.1. Study protocol No: M34100-025

An Open-Label Phase II Study of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Relapsed Following Front-Line Therapy and Are Refractory to Their Most Recent Therapy

3.2. Study design

This was an open-label, multicenter study designed to evaluate the efficacy and safety of PS-341 at a dose of 1.3 mg/m²/dose alone, or in combination with dexamethasone, in patients with MM who have relapsed following initial front-line therapy and are refractory to their most recent therapy whether or not containing systemic corticosteroids.

3.2.1 Primary Objective:

To determine the overall response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR)] following treatment with monotherapy PS-341 1.3 mg/m²/dose in patients with MM.

Reviewer comment: There are several response criteria used in the evaluation of therapy in MM. Complete responses by the Blade criteria appears to be correlated with such clinical benefit parameters such as survival and disease free survival, however the use of these criteria is

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not well established outside the context of transplantation. Literature support for the use of partial responses, (PR's "SWOG remissions" and especially minor response (MR) as surrogates for clinical benefit is less clear, particularly for the minor responses (see introduction). A definitive correlation between improved response and improved survival is difficult to demonstrate. However, based on the aggregate information available, partial responses do appear to be correlated with clinical benefit.

3.2.2 Secondary objectives

- To determine the response rate following treatment with combination therapy with PS-341 1.3 mg/m²/dose plus dexamethasone 40 mg in patients with MM who have failed to respond to or relapsed following treatment with PS-341 alone
- To assess the safety and tolerability of PS-341 1.3 mg/m²/dose alone and in combination with dexamethasone 40 mg in patients with MM
- To obtain additional pharmacodynamic information for PS-341 1.3 mg/m²/dose in patients with MM as assessed by the proteasome inhibition assay
- To obtain additional genomic information on MM and its response to drug. Special assays [e.g., interleukin-6 (IL-6)] will be done to obtain information on MM disease markers and mechanisms of action of PS-341 in this disease
- To pilot a composite quality of life (QOL) instrument in evaluating potential changes in QOL during treatment and correlating QOL to response data

3.2.3 Patient Population

3.2.3.1 Significant disease inclusion criteria

- Previously diagnosed with MM based on standard criteria (see Appendix 1)
- Relapsed following a response to standard first-line chemotherapy (e.g., VAD or MP) or first-line high-dose chemotherapy, and refractory (i.e., failure to achieve at least CR, PR, or SD) to their most recent chemotherapy, whether or not containing systemic corticosteroids

Reviewer comment: For registration on the basis of a single arm trial, the study indication should be well defined, the study population reasonably homogeneous, and ideally the indication should represent an unmet medical need. This provides for the requirement of the trials being 'well controlled.' In this case entry criteria allowed enrollment of patients who have progressed following treatment with a variety of therapies, from corticosteroids alone to multiple cycles of high dose chemotherapy with stem cell transplant.

3.2.3.2 Laboratory inclusion criteria

- Baseline platelet count $\geq 50 \times 10^9/L$, or, if the bone marrow is extensively infiltrated, $\geq 30 \times 10^9/L$
- Hemoglobin ≥ 8.0 g/dL

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- Absolute neutrophil count $\geq 1.0 \times 10^9/L$, or, if the bone marrow is extensively infiltrated, $\geq 0.5 \times 10^9/L$
- AST (SGOT): ≤ 3 times the upper limit of institutional laboratory normal
- ALT (SGPT): ≤ 3 times the upper limit of institutional laboratory normal
- Total bilirubin: ≤ 2 times the upper limit of institutional laboratory normal, unless clearly related to the disease
- Renal function: Calculated or measured creatinine clearance: ≥ 30 mL/minute
- Patients with a creatinine clearance > 10 mL/minute and < 30 mL/minute due to significant myelomatous involvement of the kidney may be enrolled in the study after receipt of approval from the medical monitor
- Serum sodium ≥ 130 mmol/L

3.2.3.3 Exclusion criteria

- POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes)
- Plasma cell leukemia
- Corticosteroids (> 10 mg/day prednisone or equivalent) within three weeks before enrollment
- Received immunotherapy or antibody or radiation therapy within four weeks before enrollment
- Receipt of localized radiation therapy does not preclude enrollment in the study
- HIV infection, hepatitis B or C viral infection

3.2.4 Treatment plan:

3.2.4.1 Initial Dose and schedule

- During the first two study drug cycles (Cycles 1 and 2), all patients will receive PS-341 $1.3 \text{ mg/m}^2/\text{dose}$.

3.2.4.2 Doses subsequent to cycle 2

- Patients who are determined to have achieved CR, PR, or MR or experience NC will again receive PS-341 $1.3 \text{ mg/m}^2/\text{dose}$ in both Cycles 3 and 4.
- Patients who are determined to have definitive evidence of PD will receive PS-341 $1.3 \text{ mg/m}^2/\text{dose}$ plus dexamethasone 40 mg in both Cycles 3 and 4.

3.2.4.3 Dose plan after completion of both Cycles 5 and 6:

- Patients who were on PS-341 $1.3 \text{ mg/m}^2/\text{dose}$ alone and are determined to have maintained a CR for at least 12 weeks (CR first documented after the end of Cycle 2) will be discontinued from study drug. (These patients will have had PS-341 for 18 weeks).

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- Patients on PS-341 alone who are determined to have achieved a new CR or still are in CR after achieving it after Cycle 4, or are determined to have PR or MR as compared with their status after Cycle 4 will receive PS-341 1.3 mg/m²/dose in Cycles 7 and 8.
- Patients on PS-341 alone who are now determined to have new PD or show NC as compared with their status at the end of Cycle 4 will receive PS-341 1.3 mg/m²/dose plus dexamethasone 40 mg in Cycles 7 and 8.
- Patients who were on PS-341 1.3 mg/m²/dose plus dexamethasone 40 mg, and who are determined to have achieved CR, PR, or MR or experienced NC again as compared with their status after Cycle 4 will receive PS-341 1.3 mg/m²/dose plus dexamethasone 40 mg in Cycles 7 and 8.
- Patients who were on PS-341 1.3 mg/m²/dose plus dexamethasone 40 mg who are determined to have PD as compared with their status at the end of Cycle 4 will be discontinued from the study.
- In this study, patients will receive a maximum of eight cycles of study drug.

3.2.5 Dose Escalation: (was not permitted)

3.2.6 Dose reduction guidelines

Before each study drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria.

- ◆ If the patient experiences febrile neutropenia, a Grade 4 hematologic toxicity, with the exception of lymphopenia, or any \geq Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug, then study drug is to be held.
- ◆ For non-hematologic toxicities, study drug is to be held for up to two weeks until the toxicity returns to Grade 1 or better.
- ◆ For hematologic toxicities, with the exception of lymphopenia, study drug is to be held for up to two weeks until the patient has a hemoglobin value \geq 8 g/dL, an ANC \geq 1.0×10^9 /L, and a platelet count $\geq 30 \times 10^9$ /L.
- ◆ Dose interruption or study discontinuation is not required for lymphopenia.
- ◆ If, after study drug has been held, the toxicity does not resolve, as defined above, then the patient must be discontinued from the study.
- ◆ If the toxicity resolves, as defined above, then PS-341 may be restarted at a reduced dose, as follows:
 - If the patient was receiving 1.3 mg/m², reduce the dose to 1.0 mg/m²
 - If the patient was receiving 1.0 mg/m², reduce the dose to 0.7 mg/m²
 - If the patient was receiving 0.7 mg/m², discontinue the patient from the study
 - Dose reductions below 0.7 mg/m² are not allowed.

3.3. Concomitant treatment

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Permitted medications and treatments

- Bisphosphonates
- Erythropoietin
- Granulocyte growth factors or granulocyte colony stimulating factor
- Immunoglobulin infusions
- Blood products
- Plasmapheresis

Excluded medications

- Corticosteroids (≥ 10 mg prednisone or equivalent)
- Any investigational agent other than PS-341
- Radiation therapy

If localized radiation therapy is, the investigator's opinion, required for the treatment of cancer complications, then this therapy must be discussed in advance with the medical monitor.

3.4. Removal from study

Patients will be informed that they have the right to discontinue from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to discontinue patients from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- Missing three or more study drug doses within a treatment cycle due to toxicity
- Maintenance of CR for 12 weeks while receiving PS-341 1.3 mg/m²/dose alone
- Patient request
- Lack of efficacy
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up

At the time of discontinuation, all study procedures outlined for the End of Study visit should be completed. The reason(s) for a patient's discontinuation from the study are to be recorded on the CRF.

3.4.1 Efficacy Analysis: Schedule

Assessment of disease response will be performed on Day 1 of Cycles 3, 5, and 7; and at the End of Study visit. The primary efficacy analysis will be performed on the ITT population rate of responders, where a responder is defined for this analysis as a patient who achieves a CR, PR or MR from PS-341 alone. If a patient is determined to have CR, PR, or MR, then assessment of disease response is to be performed six weeks later to confirm the response.

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3.4.2 Independent Review Committee

The Independent Review Committee (IRC) consisted of three physicians with expertise and experience in the diagnosis and management of MM but without direct involvement in the conduct of the study. The IRC members performed independent majority review of selected data collected in this study in order to assess each patient's disease response, based on the criteria reported by SWOG and Blade et al, (see Table 3). Patients with non-measurable disease (i.e., nonsecretory or oligosecretory MM) at the Screening visit will be excluded from the IRC review.

3.5... Primary Efficacy Analysis

The primary objective was to determine the overall response rate [the combined complete response (CR) + partial response (PR) + minimal response (MR)] following treatment with monotherapy PS-341 1.3 mg/m²/dose in patients with MM.

3.5.1 Complete Response:

A complete response (CR) required all of the following

- Disappearance of the original monoclonal protein from the blood and urine on at least two determinations for a minimum of six weeks by immunofixation studies
- <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks
- No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response)
- Disappearance of soft tissue plasmacytomas for at least six weeks

3.5.2 Partial Response

Partial response (PR) required all of the following:

- ≥50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart
- If present, reduction in 24-hour urinary light chain excretion by either ≥90% or to <200 mg for at least two determinations six weeks apart
- ≥50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

3.5.3 Minimal response (MR)

Minimal Response (MR) required all of the following:

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- $\geq 25\%$ to $\leq 49\%$ reduction in the level of serum monoclonal protein for at least two determinations six weeks apart
- If present, a 50 to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for at least two determinations six weeks apart
- 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for at least six weeks
- No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

3.5.4 Progressive disease (for patients not in CR)

Progressive Disease (PD) required one or more of the following:

- $>25\%$ increase in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation
- $>25\%$ increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation
- $>25\%$ increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%
- Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas
- Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture)
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)

3.5.5 Relapse from CR

Relapse from CR required at least one of the following:

- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least one follow-up and excluding oligoclonal immune reconstitution
- $\geq 5\%$ plasma cells in the bone marrow aspirate or biopsy
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture)
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)

3.6. Summary of Response Criteria

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In a pre-NDA meeting on Sept 4 2002 , the sponsor was requested to provide "...evidence to demonstrate that the results of your phase 2 study are reasonably likely to predict clinical benefit, given the historical lack of correlation between response rates and survival in myeloma trials, and to "Describe complete response rates with respect to Blade and the old SWOG criteria and clearly distinguish which patients were treated with dexamethasone." The sponsors proposed an efficacy analysis based on 5 categories of response: Minor responses, Partial Responses, Remission^{SWOG}, CR^{IF+} and CR^{Blade}. The following Table summarizes the differences between response categories:

Table 6: Remission Criteria Used in the efficacy analysis of Study M34100-025

Response Category	IF	Reduction of M protein required		Bone Marrow	Bone Disease	Serum Calcium	Confirmation required?
		SPEP	UPEP				
CR ^{Blade}	Negative	100%	100%	<5% PC	Stable	Normal	Yes (6 weeks)
CR ^{IF+}	NR	100%	100%	NR	Stable	Normal	Yes (6 weeks)
Remission ^{SWOG}	NR	75%	90%	NR	Stable ^a	Normal ^a	Yes (3 wks) ^a
PR	NR	50%	90%	NR	Stable	NR	Yes (6 weeks)
MR	NR	25%	50%	NR	Stable	NR	Yes (6 weeks)

SPEP = serum protein electrophoresis, UPEP = urine protein electrophoresis, IF = immunofixation, PC = plasma cells, PR = Partial response, MR= minimum response, ND = Not done, NR=Not required, a SWOG criteria do not require stable bone disease or normal calcium levels and confirmation of response is required at 3 weeks. However, as the IRC assessed patients based on Blade criteria, these were utilized for response assessment. CR^{Blade}: From Blade, et al. ⁽¹⁵⁾ Remission^{SWOG} See Salmon et. al ²³

Reviewer comment: The CR Blade response criteria may be considered to be evidence of clinical benefit, since durable complete remissions are considered to be evidence of clinical benefit.¹ However, this has not yet been validated for registration in myeloma indications. Remission^{SWOG} criteria have been frequently reported in the literature.²⁴ Other categories of response are less well correlated with clinical benefit, but were judged to be surrogates 'reasonably likely to predict' clinical benefit, based on a benefit analysis of these patients, literature review, and discussion with ODAC consultants. See introduction section for a discussion of different response criteria and their relation to clinical benefit.

3.7. Secondary Endpoints

3.7.1 Quality of Life parameters

QOL instruments will be completed by the patient at the Screening visit; on Day 1 of Cycles 3, 5, and 7; and at the End of Study visit. QOL instruments will be provided in the study manual. After the End of Study visit, these evaluations are to be performed on an every six-week basis only until development of confirmed PD (or relapse) for patients who have not experienced confirmed PD (or relapse) on their most recent study drug regimen (PS-341 alone or PS-341 plus dexamethasone).